Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline.

Bibliographic Source(s)

Practice Committee of the American Society for Reproductive Medicine. Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline. Fertil Steril. 2017 Sep;108(3):426-41. [80 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
NO	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
UNKNOWN	Multidisciplinary Group
UNKNOWN	Methodologist Involvement

	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
	Search Strategy
	Study Selection
	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
	Grading the Quality or Strength of Evidence
	Benefits and Harms of Recommendations
	Evidence Summary Supporting Recommendations
	Rating the Strength of Recommendations
	Specific and Unambiguous Articulation of Recommendations
	External Review
	Updating

Recommendations

Major Recommendations

Definitions for the level of evidence (Level I-III) and strength of the recommendations (Grade A-C) are given at the end of the "Major Recommendations" field.

Does Metformin Alone as First-Line Ovulation Induction Therapy Improve Clinical Pregnancy and Live-birth Rates Compared with Placebo?

Summary Statements

> There is good evidence that metformin alone vs. placebo increases the ovulation rate in women with polycystic ovary syndrome (PCOS). (Grade A)
> There is insufficient evidence to suggest that metformin alone increases pregnancy rates or live-birth rates compared with placebo. (Grade C)

Does Metformin Alone as First-line Ovulation Induction Therapy Improve Clinical Pregnancy and Live-birth Rates Compared with Clomiphene Citrate (CC)?

Summary Statement

There is fair evidence from one large, well-designed randomized controlled trial (RCT) that metformin alone is less effective than CC alone for the achievement of ovulation induction, clinical pregnancy, and live birth in women with PCOS. (Grade B)

Does Metformin Alone as First-line Ovulation Induction Therapy Improve Clinical Pregnancy and Live-birth Rates Compared with Letrozole Alone?

Summary Statements

> There is insufficient evidence to suggest that metformin alone increases pregnancy or live-birth rates compared with letrozole alone. (Grade C)
> However, there is fair evidence based on one well-designed trial in support of letrozole for ovulation induction (Grade B). Therefore, letrozole is a reasonable first-line agent for ovulation induction in PCOS patients.

When Used in Combination with Other Agents as First-line Therapy for Ovulation Induction in Women with PCOS, Does Metformin Increase Pregnancy Rates and Live-birth Rates?

Summary Statements

> There is good evidence that metformin in combination with CC improves ovulation and clinical pregnancy rates but does not improve live-birth rates compared with CC alone in women with PCOS. (Grade A)
> There is fair evidence from one RCT that pretreatment with metformin for at least 3 months followed by the addition of another ovulation-inducing drug increases live-birth rate. (Grade B)

Does the Combination of Metformin and CC or Other Ovulation Induction Agents Improve Ovulation, Clinical Pregnancy Rate, or Live-birth Rate in the Subset of CC-resistant Patients with PCOS?

CC-Metformin Versus CC Alone

Summary Statement

There is fair evidence that CC-metformin improves ovulation and pregnancy rates compared with CC alone in CC-resistant PCOS women (Grade B). However, more studies are needed to determine whether there may be subgroups of women (e.g., specific body mass index [BMI], ethnicity, absence of insulin resistance, etc.) with PCOS and CC resistance for which CC-metformin provides the most benefit over CC alone.

Metformin Versus Laparoscopic Ovarian Drilling (LOD)

Summary Statements

> There is fair evidence that overall pregnancy rates are not different with CC-metformin, CC-LOD, or LOD alone in women with CCâ€'resistant PCOS. (Grade B)
> There is insufficient evidence regarding pregnancy rate or live-birth rate with the use of metformin alone compared with LOD for ovulation induction in CCâ€'resistant PCOS patients. (Grade C)

CC-Metformin Versus Aromatase Inhibitors

Summary Statement

There is insufficient evidence to compare metformin plus CC to aromatase inhibitors alone or metformin plus aromatase inhibitors for ovulation induction in CCâ€'resistant women. (Grade C)

CC-Metformin Versus Gonadotropins

Summary Statement

There is insufficient or conflicting evidence regarding metformin use combined with CC compared with gonadotropins for ovulation induction in women with CCâ€'resistant PCOS. (Grade C)

Does Pre-pregnancy Use of Metformin Reduce the Risk of Miscarriage in Non-assisted Reproductive Technology (Non-ART) Pregnancies?

Summary Statements

There is fair evidence that metformin used while attempting pregnancy and stopped at the initiation of pregnancy does not affect the rate of miscarriage. (Grade B)
There is insufficient evidence to recommend metformin during pregnancy to reduce the chance of miscarriage. (Grade C)

Does Metformin Affect the Likelihood of Multiple Pregnancies?

Summary Statements

There is good evidence that metformin alone does not increase the rate of multiple pregnancy. (Grade A)
While there is no evidence of an effect (either increase or decrease) on multiple pregnancy rates in cycles using combination CC plus metformin vs. CC alone, there remains insufficient data on this matter due to lack of adequate power to detect a difference. (Grade C)
There is insufficient evidence of a reduced risk for multiple pregnancy with the addition of metformin to follicle-stimulating hormone (FSH) compared with FSH alone. (Grade C)

Is Metformin More Effective in Lean or Obese PCOS Patients?

Summary Statement

There is insufficient good-quality evidence to determine if metformin is more effective in non-obese or obese women with PCOS. (Grade C)

Recommendations

Metformin alone should not be used as first-line therapy for ovulation induction in women with PCOS, since ovulation induction agents such as CC or letrozole are more effective. CC alone or letrozole alone are reasonable first-line agents for ovulation in women with PCOS. Combination therapy with CC may be beneficial in women who are resistant to CC alone. While metformin alone is not likely to increase live-birth rate in women seeking pregnancy in the short term, utilizing metformin in individualized cases of PCOS with the goal of improving ovulation rates over the long term may be of benefit. In the context of increased ovulation rate and overall improved insulin resistance on metformin, the subsequent addition of other ovulation-inducing agents may be beneficial in increasing pregnancy rates, although there is insufficient evidence of an increase in live-birth rates. These data suggest that individualization of treatment may be warranted, particularly in younger women with PCOS. Additional large, adequately powered randomized trials are needed in carefully defined populations of women with various forms of PCOS (i.e., phenotype specified) to determine in whom the use of metformin may be of benefit.

Definitions

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions based on clinical experience, and reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Infertility
- Polycystic ovary syndrome (PCOS)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide recommendations for the use of metformin for ovulation induction in women with polycystic ovary syndrome (PCOS) desiring pregnancy

Target Population

Women with polycystic ovary syndrome (PCOS) desiring pregnancy

Interventions and Practices Considered

Ovulation Induction Therapy

- Metformin
- Clomiphene citrate (CC)
- Letrozole
- Other ovulation induction agents
  - Laparoscopic ovarian drilling (LOD)
  - Aromatase inhibitors
  - Gonadotropins
- Combination therapies

Major Outcomes Considered

- Ovulation
- Clinical pregnancy rate
- Multiple pregnancy rate
- Miscarriage rate
- Live-birth rate

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This clinical practice guideline was based on a systematic review of the literature performed in the electronic database MEDLINE through PubMed on December 7, 2016. No limit or filter was used for time period covered or language, but articles were subsequently culled for English language.

A combination of the following medical subject headings or text words were used: aromatase inhibitors, clomiphene, dexamethasone, diathermy, diathermy/methods, female, fertility agents, follicle aspiration, follicle puncture, follicle stimulating hormone/therapeutic use, glucocorticoids, gonadotropin releasing hormone/therapeutic use, gonadotropins/ therapeutic use, insulin sensitizer, intrauterine insemination, in vitro maturation, in vitro oocyte maturation techniques, IUI, IVM, laser therapy/methods, laser therapy/therapeutic use, letrozole, Leventhal, metformin, ovarian drilling, ovulation induction/adverse effects, ovulation induction/methods, PCO, PCOD, polycystic ovar$, polycystic ovarian syndrome/ drug therapy, polycystic ovary syndrome/drug therapy, selective estrogen receptor modulators, Stein-Leventhal.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed to develop inclusion/exclusion criteria (see Table 1 in the original guideline document). Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, ovulation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles.

Four members of an independent task force reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and resolved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

Number of Source Documents

The electronic search and examination of reference lists from primary and review articles yielded 1,017 studies, of which 73 studies were included.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Descriptive studies, case series, case reports, letters, nonsystematic .reviews, opinions based on clinical experience, and reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The level of the evidence was evaluated using the grading system found in the "Rating Scheme for the Strength of the Evidence" field and is assigned for each reference in the bibliography (see the original guideline document).

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The literature was reviewed to answer the following questions:

- Does metformin alone as first-line ovulation induction therapy improve clinical pregnancy and live-birth rates compared with placebo?
- Does metformin alone as first-line ovulation induction therapy improve clinical pregnancy and live-birth rates compared with clomiphene citrate (CC)?
- Does metformin alone as first-line ovulation induction therapy improve clinical pregnancy and live-birth rates compared with letrozole alone?
- When used in combination with other agents as first-line therapy for ovulation induction in women with polycystic ovary syndrome (PCOS), does metformin increase pregnancy rates and live-birth rates?
- Does the combination of metformin and CC or other ovulation induction agents improve ovulation, clinical pregnancy rate, or live-birth rate in the subset of CC-resistant patients with PCOS?
- Does pre-pregnancy use of metformin reduce the risk of miscarriage in non-assisted reproductive technology (non-ART) pregnancies?
- Does metformin affect the likelihood of multiple pregnancies?
- Is metformin more effective in lean or obese PCOS patients?

The strength of the recommendations was evaluated using the grading system found in the "Rating Scheme for the Strength of the Recommendations" field.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document was reviewed by American Society for Reproductive Medicine members and their input was considered in the preparation of the final document.

The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each summary statement that supports the recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Beginning in the 1990s, a series of studies involving relatively small numbers of women with polycystic ovary syndrome (PCOS), many uncontrolled and some controlled, indicated that metformin reduced insulin resistance in women with PCOS and increased the likelihood of ovulation and pregnancy without, or sometimes with, clomiphene citrate.
- While metformin alone is not likely to increase live-birth rate in women seeking pregnancy in the short term, utilizing metformin in individualized cases of PCOS with the goal of improving ovulation rates over the long term may be of benefit.
- In the context of increased ovulation rate and overall improved insulin resistance on metformin, the subsequent addition of other ovulation-inducing agents may be beneficial in increasing pregnancy rates, although there is insufficient evidence of an increase in live-birth rates.

Refer to the original guideline document for details about potential benefits of specific interventions.

Potential Harms

Therapy with metformin does not lead to weight gain and may be associated with modest weight loss, largely because of a slight anorectic effect as well as gastrointestinal side effects, including abdominal discomfort, diarrhea, nausea, and vomiting. Importantly, metformin may be associated with the development of lactic acidosis, but almost all patients who develop acidosis have impaired renal function, and the incidence is rare when the drug is used appropriately.

Refer to the original guideline document for details about potential harms of specific interventions.

Qualifying Statements

Qualifying Statements

- This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations.
- Refer to the "Limitations of the Literature" section in the original guideline document.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Practice Committee of the American Society for Reproductive Medicine. Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline. Fertil Steril. 2017 Sep;108(3):426-41. [80 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Sep

Guideline Developer(s)

American Society for Reproductive Medicine - Nonprofit Organization

Source(s) of Funding

American Society for Reproductive Medicine (ASRM)

Guideline Committee

Practice Committee of the American Society for Reproductive Medicine (ASRM)

Composition of Group That Authored the Guideline

Committee Members: Alan Penzias, MD; Kristin Bendikson, MD; Samantha Butts, MD, MSCE; Christos Coutifaris, MD, PhD; Tommaso Falcone, MD; Gregory Fossum, MD.; Susan Gitlin, PhD; Clarisa Gracia, MD, MSCE; Karl Hansen, MD, PhD; Andrew La Barbera, PhD; Jennifer Mersereau, MD; Randall Odem, MD; Richard Paulson, MD; Samantha Pfeifer, MD; Margareta Pisarska, MD; Robert Rebar, MD; Richard Reindollar, MD; Mitchell Rosen, MD; Jay Sandlow, MD; Michael Vernon, PhD

Guideline Task Force Members: Heather Huddleston, MD; Emily Jungheim, MD; Laura Tatpati, MD; and Carter Owen, MD

Financial Disclosures/Conflicts of Interest

All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the American Society for Reproductive Medicine (ASRM) Web site .

Availability of Companion Documents

Continuing medical education (CME) credit related to this guideline is available from the American Society for Reproductive Medicine (ASRM) Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 29, 2017. The information was verified by the guideline developer on December 21, 2017.

This NEATS assessment was completed by ECRI Institute on October 23, 2017. The information was verified by the guideline developer on December 21, 2017.

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